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CALCIUM HOMEOSTASIS IN UNTREATED PULMONARY TUBERCULOSIS I–BASIC STUDY

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This study has been done to evaluate serum calcium, phosphorus (P), magnesium, parathyroid hormone (PTH), calcitonin (CT), and cyclic adenosine monophosphate (cAMP) in recently diagnosed pulmonary tuberculous patient, (n=61) and the results were compared with the healthy control group (n=22). Twenty four hours urine was collected for estimation of these electrolytes as well as cAMP. Nephrogenous cAMP (NcAMP) was calculated. Serum Ca and PTH were significantly reduced in TB groups, but CT was elevated. Serum Mg, P and cAMP as well as urinary Ca and Mg in TB groups were similar to that of the control group. Urinary P, cAMP NcAMP were increased in patient groups compared with the control.

The reduced serum Ca could be due to impaired intestinal absorption of Ca, or deficient intake as a result of anorexia, decreased plasma albumin, decreased active metabolites of vitamin D or elevated CT.

The rise in serum CT in TB might be due to increased CT secreted from the bronchial K–cells. Increased NcAMP might be due to the associated increase in serum antidiuretic hormone (ADH). The elevated urinary P in TB could be attributed to tissue breakdown, decreased serum PTH or increased CT.

Key words : Tuberculosis, Parathyroid hormone, Calcitonin, Calcium, Phosphorus, Magnesium, Cyclic adenosine monophosphate

INTRODUCTION

Patients with pulmonary tuberculosis tend to have a total plasma calcium concentration lower than normal (1), (2), probably due to malnutrition and gastrointestinal disturbance. High levels of serum calcium were reported by other authors (3—8).

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This study has been planned to investigate and evaluate total calcium, magnesium and inorganic phosphorus metabolism in a group of patients initially diagnosed as having active pulmonary tuberculosis before specific or adjuvant drug intake, in order to gain a clear picture about the metabolism of these elements in tuberculous patients. Calcitonin (CT) and parathormone (PTH), the regulatory hormones of these elements were also estimated.

MATERIAL AND METHODS

Eighty-three subjects constituted the material of this work. All were males. They were classified into two groups : Healthy control group (group I, n=22), aged 20-56 years. Tuberculous group (group II, n=61) with active pulmonary tuberculosis aged 18-66 years. They were subclassified according to National Tuberculosis Association (9) into : Group IIa : Moderately advanced lesions (n=30) and Group IIb : Far-advanced lesions (n=31).

The healthy control subjects were selected from the working staff of Benha and Abbassia Chest Hospitals. Clinical and laboratory investigations were performed for each to exclude tuberculosis or other diseases.

In group II, full history taking, clinical, radiological and laboratory examinations were done. Their sputum was positive for acid-fast bacilli, but other investigations showed only non-associated diseases.

All patients and normal control subjects were subjected to an identical study protocol. Urine was collected over 24 hours in bottles containing 6 N HCl (1 m*l*/h of collection) as preservative (10). 24-hour urine volume was measured, and aliquots taken therefrom were centrifuged and the supernatants were kept frozen at −20°C until assay.

Fasting venous blood was collected for serum separation which was partly kept frozen at −20°C for RIA determination of PTH (11), CT (12) and cAMP (13), and partly for colorimetric determination of total calcium (14), (15), inorganic phosphorus (16) and creatinine (17).

Urinary and nephrogenous cAMP were expressed as a function of glomerular filtration rate according to Broadus et al. (18).

The data obtained were statistically analysed by the Student's "t" test.

Table 1. Statistical analysis of serum PTH and calcitonin (CT), total calcium (Ca), magnesium and inorganic phosphorus (Pi) in normal controls and tuberculous patients.

GROUP	Parameter	PTH pg/m*l*	CT pg/m*l*	Ca. mg/d*l*	Mg. mg/d*l*	Pi mg/d*l*
Normal control (group I) n = 22	Mean	146	98	11.1	2.66	4.24
	SE ±	5.7	4.5	0.31	0.09	0.08
Tuberculous patients with moderately advanced lesions (group IIa) n = 30	Mean	114	132	9.2	2.41	4.45
	SE ±	9.8	5.9	0.33	0.12	0.12
	P_1	<0.01	<0.001	<0.001	>0.05	>0.05
Tuberculous patients with far-advanced lesions (group IIb) n = 31	Mean	106	142	9.1	2.36	4.48
	SE ±	8.5	8.2	0.29	0.14	0.15
	P_1	<0.001	<0.001	<0.001	>0.05	>0.05
	P_2	>0.05	>0.05	<0.05	>0.05	>0.05

P_1 : results compared to the control group (group I)

P_2 : results compared to tuberculous group with moderately advancd lesions (group IIa).

Table 2. 24-Hour Urinary Calcium (Ca), Magnesium (Mg) inorganic phosphorus and cAMP; serum and nephrogenous cAMP in Normal Controls and Tuberculous Patients.

GROUP	PARAMETER	Ca mg/24h	Mg mg/24h	Pi mg/24h	Serum cAMP n mol/dl	U cAMP n mol/ dl GF	NcAMP n mol/ dl GF
Group I	Mean	164	123	630	0.99	4.22	3.22
	SE ±	14.7	9.4	31	0.08	0.30	0.27
Group IIa	Mean	169	122	1180	0.87	6.04	5.17
	SE ±	10.3	7.5	61	0.05	0.81	0.82
	P_1	>0.05	>0.05	<0.001	>0.05	<0.025	<0.025
Group IIb	Mean	171	116	1400	0.78	6.68	5.90
	SE ±	12.7	5.5	68	0.08	0.62	0.65
	P_1	>0.05	>0.05	<0.001	>0.05	<0.001	<0.001
	P_2	>0.05	>0.05	<0.01	>0.05	>0.05	>0.05

P_1 : results compared to the control group (group I)
P_2 : results compared to tuberculous group with moderately advanced lesions (group IIa).
UcAMP : Urinary cAMP inn mol/dl glomerular filtrate (GF).
NcAMP : Nephrogenous cAMP in nmol/dl glomerular filtrate.

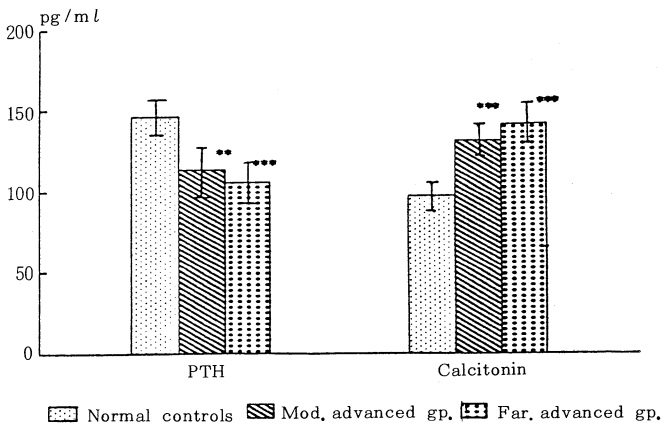

Fig. 1. Serum Levels of PTH and Calcitonin in Normal Controls and Tuberculous Patients. (Mean ± SEM)

RESULTS

The results are given in Tables (1-2) and Fig. (1-4).

DISCUSSION

In this study serum calcium levels showed a highly significant decrease in tuberculous patients (group II a & b) than in healthy controls ($P<0.001$). This result is in agreement with Davies et al. (1) and Salem et al. (2). The reduction in serum calcium level in this study may be attributed to the rise of calcitonin in tuberculous patients (both groups) and deficiency of parathyroid hormone in the same groups of patients ($P<0.001$). Hypercalcitoninaemia decreases calcium absorption from the intestine and calcium mobilisation from bone

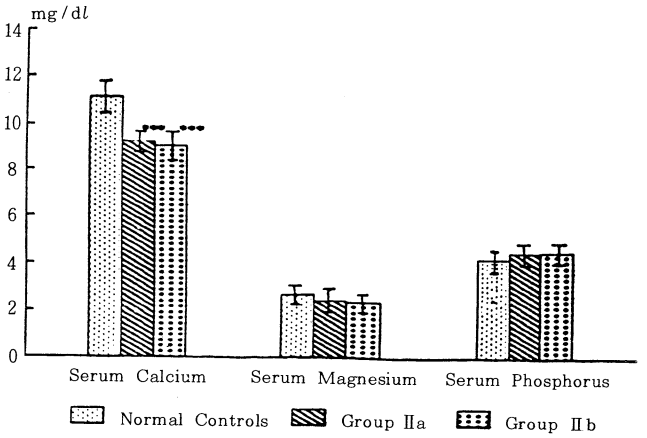

Fig. 2. Serum Levels of Calcium, Magnesium and Phosphorus in Normal Controls and Tuberculous Patients. (Mean ± SEM)

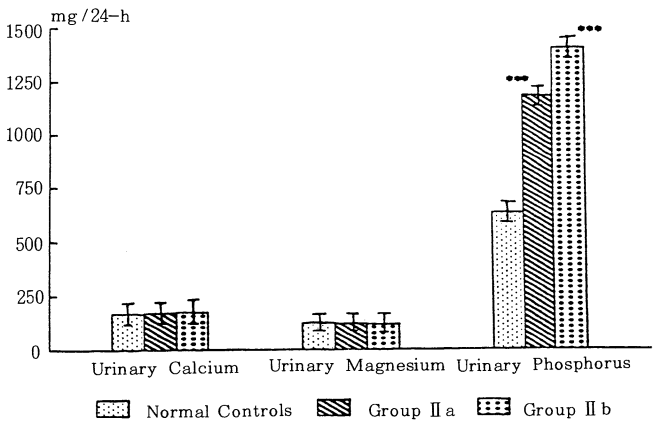

Fig. 3. 24-h Urinary Calcium Magnesium and Phosphorus in Normal Controls and Tuberculous Patients. (Mean ± SEM)

and increased calcitonin lead to decreased serum calcium which is potentiated by reduced serum PTH levels in our patients.

Albumin is the principal Ca-binding factor in plasma ; hence reduction of plasma albumin could contribute to decreased serum total calcium. Hypoalbuminaemia is commonly reported in cases with pulmonary tuberculosis (1), (19), due to poor appetite, lack of adequate protein intake, associated fever and/or derangement of hepatic synthesis. In these studies impairement of gastrointestinal function in pulmonary tuberculosis was not recorded.

Decreased plasma concentration of 25-hydroxycholecalciferol in untreated tuberculosis was reported by Davis et al. (1). It is the precursor of 1,25-dihydroxycholecalciferol which promotes elevation of serum calcium absorption. Singhellakis et al. (20) attributed hypocalcaemia in pulmonary tuberculosis to impaired Ca absorption from GIT.

Our results concerning serum calcium in

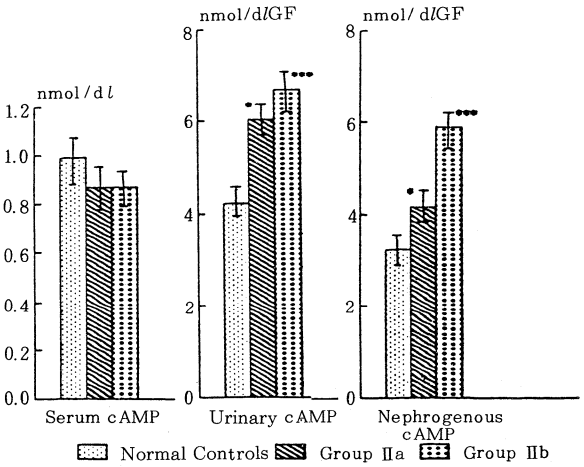

Fig. 4. Serum, Urinary (total), and Nephrogenous cAMP in Normal Controls and Tuberculous Patients. (Mean ± SEM)

tuberculosis disagree with that of Need et al. (3) ; Kitrou et al. (5) ; Ojwang et al. (6) and Gomaa (7) who reported hypercalcaemia in pulmonary tuberculosis. Antituberculous drugs and supplementation of vitamin D were suggested to be the cause of hypercalcaemia (21), (22). Abbasi, et al. (23) suggested that increased sensitivity to vitamin D in TB is similar to that observed in sarcoidosis. Our patients neither received antituberculous treatment nor vitamin D supplements before the study.

Kipnis and Raju (24) attributed hypercalcaemia of tuberculosis to hyperparathyroidism but against this hypothesis is the fact that corticosteroids have been used with success in a single case of disseminated bone tuberculosis (25), and that serum parathyroid hormone levels were highly significantly decreased in this study.

The basal 24-h urinary excretion of calcium was insignificantly higher in tuberculous patients (both groups) compared to the normal control group ($P<0.05$). This finding was in agreement with Singhellakis et al. (20) but disagreed with Shai et al. (21) and Johnson and Shneerson (26) who reported significant hypercalciuria in tuberculous patients, but their patients were receiving vitamin D supplements.

Reduced serum Ca in TB groups should be associated with decreased Ca in glomerular filtrate, particularly in the presence of low PTH serum levels whereas calcitonin increases renal clearence of calcium by decreasing renal tubular reabsorption (27), thus promoting urinary excretion of Ca. These factors might be so balanced that ultimate urinary Ca remained unchanged in TB.

Evaluation of serum calcitonin in tuberculous patients with moderately advanced and far-advanced lesions showed a highly significant increase ($P<0.001$) compared to the normal control group, and non-significant changes on comparing TB subgroups against each other. Similar findings were obtained by Becker et al. (28) ; El-Giridly (29) and Gomaa (7). Becker et al. (28) had suggested that a specific endocrine role for the bronchial cell and stated that this may explain the high levels of serum calcitonin in patients with inflammatory lung diseases including tuberculosis. From this finding, the sequence of events would begin with increased CT secretion from the bronchial K-cells, with subsequent reduction of serum calcium. There may be other factors suppressing PTH secretion, and thus counteracting correction of serum Ca.

With onset of efficient therapy these cells activity is supposed to be inhibited, resuming normal values of CT, Ca as well as PTH.

El-Giridly (29) and Gomaa (7) stated that, serum PTH was to be elevated along with hypercalcaemia in treated patients, but Singhellakis et al. (30) reported unchanged serum PTH before and during treatment of tuberculous patients.

In this study, there is an insignificant decrease in serum magnesium in tuberculous patients (group II a & b) compared to the normal control group and insignificant changes among the tuberculous subgroups.

This result is in agreement with the study by Curiel et al. (8) and Salem et al. (2), but El-Giridly (29) and Gomaa (7) observed hypomagnesemia in active pulmonary tuberculous patients during treatment with specific drugs, while hypermagnesemia was evident in the healed group.

Thorough search in the literature revealed no previous study on magnesium excretion in tuberculosis to compare with.

Twenty-four hour urinary magnesium excretion is unchanged in TB versus the control group. This finding could be explained on the same basis as that used for the explanation of the behaviour of urinary Ca. Serum phosphorus levels in the groups of tuberculous patients with moderately advanced and far-advanced lesions showed insignificant changes from those in the normal control group. This result is in agreement with Shai (21) ; Abbasi et al. (23) and Curiel et al. (8). In a study by Ojwang et al. (6) hyperphosphatemia was reported in association with hypercalcaemia in tuberculous patients under treatment.

The effect of decreased serum PTH and hypercalcitoninaemia on phosphorus metabolism is presented by insignificantly elevated serum and urinary levels of phosphorus in the tuberculous subgroup ($P<0.001$). Urine phosphorus per 24 hour in far-advanced cases is higher than that in moderately advanced cases ($P<0.01$), so that the degree of hyperphosphaturia is in parallel to the severity of the lesion ; hyperphosphaturia is more prominent in the group of patients with far-advanced lesions which could be attributed to the increased amount of phosphate released by destroyed tissues. Furthermore, calcitonin, being a phosphaturic agent (31) may contribute to increased urinary phosphate in tuberculosis. Low serum concentrations of 25-hydroxycholecalciferol in untreated tuberculosis reported by Davies et al. (1) may lead to increased urinary excretion of phosphorus.

Total and nephrogenous cAMP were slightly significantly elevated in tuberculous patients with moderately advanced lesions ($P<0.025$) and highly significantly elevated in the group with far-advanced lesions, compared to the normal control group ($P<0.001$).

The increase in total and nephrogenous cAMP in the TB subgroup could be due to the effect of anti-diuretic hormone (ADH) which is secreted inapporiately in patients with pulmonary tuberculosis as reported by Weiss and Katz (32). ADH is one of the stress hormones that might be elevated in the distressing tuberculous lesions. Increases in urinary cAMP have been reported in patients with the syndrome of inappropriate antidiuretic hormone secretion (33).

Nephrogenous as well as urinary cAMP are secondary to the effect of PTH and ADH on tubular cells. Serum PTH, being reduced in TB subgroups vs control, yet the effect of ADH remains.

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